REMARKS

Claims 1-11 are pending. The November 19, 2008 Amendment After Final was entered by the Examiner. *See,* December 23, 2008 Advisory Action.

I. The rejection of claims 1-9 and 11 under 35 U.S.C. § 103(a) as obvious over Geusens et al., J of Clin Densitometry, 2001;4:389-394

The Examiner has maintained the rejection of claims 1-9 and 11 as obvious over Geusens et al., J of Clin Densitometry, 2001;4:389-394 ("Geusens"). According to the Examiner, Geusens discloses the case history of an 18-year old boy treated with intravenous pamidronate (a bisphosphonate) for extreme back pain resulting from multiple vertebral fractures. The pamidronate was administered intermittently over a nine month period. The patient's back pain progressively improved. *See,* October 15, 2008 Office Action, page 3.

The Examiner acknowledges that Geusens does not teach treating chronic spinal mechanical pain, i.e., any back pain lasting more than twelve weeks which is not caused by cancer or an osteoporotic compression fracture. However, the Examiner contends that it would have been obvious to use pamidronate for the treatment of any back pain because Geusens discloses the effectiveness of pamidronate in pain management. *Id.* at 3-4. The Examiner was not persuaded by applicant's argument in the Amendment After Final. Applicant respectfully traverses this rejection.

According to the Examiner: "Applicant does not disagree that the Geusens [sic] did have an improved [sic] in his pain comprising administration of pamidronate in relation to bone density." Respectfully, this misstates applicant's argument. Applicant did not argue that pamidronate was administered to treat pain, i.e., the pain treatment did not "comprise" pamidronate. Applicant stated that: "bisphosphonates, including pamidronate, are only mentioned in Geusens in relation to bone density. The patient in Geusens did have an improvement in his pain, but other treatments he received, alone or in combination, can account for this improvement;" and "[t]he instant obviousness rejection should be withdrawn because every mention of bisphosphonates in Geusens is made in relation to bone density, not pain." Amendment After Final, p. 4.

The Examiner contends that the instant claims are obvious because they include the open-ended transitional phrase "comprising." Thus, the claims do not exclude administering additional therapies for pain, such as those described in Geusens (i.e., calcium, vitamin D, calcitonin, physiotherapy, progressive mobilization, glucocorticoids, analgesics, and nonsteroidal anti-inflammatory drugs). *See*, Advisory Action.

Applicant agrees that the claims are open-ended. However, the claims are directed to administering a bisphosphonate for the relief of chronic spinal mechanical pain. No combination of the references teaches this feature. In *KSR*, the Supreme Court stated "the need for caution in granting a patent based on the combination of elements found in the prior art." *KSR International Co. v. Teleflex Inc. (KSR)*, 82 USPQ2d 1385, 1395 (2007). Further, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 1395. The Supreme Court provided *Sakraida v. AG Pro, Inc.*, as an example of this principle: "the Court derived . . . the conclusion that when a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." Id. at 1395-96 (internal quotations omitted.). *See*, MPEP 2141. The instant claims are non-obvious because administering a bisphosphonate to relieve chronic spinal mechanical pain is not "an element found in the prior art," "a known method," or an "old element." No combination of the references discloses, suggests, or renders predictable administering a bisphosphonate to treat spinal mechanical pain. The references merely disclose the well-known use of bisphosphonates for increasing bone density.

Accordingly, for the reasons stated above, this rejection should be withdrawn.

II. The rejection of claims 1-9 and 11 under 35 U.S.C. § 103(a) as obvious over Urban et al., Society for Neuroscience Abstracts, 2001;27(1):1326 in view of U.S. Patent No. 6,676,970

The Examiner has maintained the rejection of claims 1-8, 10 and 11 as obvious over Urban et al., Society for Neuroscience Abstracts, 2001;27(1):1326 ("Urban") in view of U.S. Patent No. 6,676,970 ("Bader"). According to the Examiner, Urban discloses that zoledronate (a bisphosphonate) produces an anti-allodynic effect in rats, and Bader discloses parental zoledronate

preparations. The Examiner contends that one of ordinary skill in the art would have been motivated to use intravenous zoledronate to treat pain as an alternative to the subcutaneous formulation disclosed in Urban. *See,* Office Action, pages 4-5. The Examiner was not persuaded by applicant's argument in the Amendment After Final. According to the Examiner, "Urban et al. teach that the bisphosphonate, zoledronate produced a significant anti-allodynic effect in rats, this would motivate one of ordinary skill in the art toe [sic] employ zoledronic acid for the treatment of pain." Advisory Action. Applicant respectfully traverses this rejection.

This response is accompanied by a Second Declaration of Dr. Marco Pappagallo Under 37 C.F.R. 1.132 ("Second Pappagallo Dec."). Dr. Pappagallo is the inventor of the instant invention, the Director of Pain Medicine Research and Development at Mount Sinai School of Medicine, and a Professor of Anesthesiology at Mount Sinai School of Medicine. Dr. Pappagallo completed his neurology residency in 1990 and his pain medicine fellowship in 1993. Dr. Pappagallo has practiced as an attending physician since 1993.

Urban discloses that intra-tibial injections of breast tumor cells produced "severe damage to the bone," and zoledronate administration resulted in the death of tumor cells. Urban, abstract. As stated in the Amendment After Final, the anti-tumor effect of bisphosphonates was known in the art at the time the instant application was filed. *See,* Second Pappagallo Dec. at 12; Green JR, Cancer Supplement, 2003;97(3):840-847 (citing publications dated between 1997-2001) (copy attached in the Amendment After Final).

According to Dr. Pappagallo, as viewed by one of ordinary skill in the art at the time the instant application was filed:

- It was well-known in the fields of oncology and pain management that a bisphosphonate can have an anti-tumor effect. Second Pappagallo Dec. at 12.
- It was known in the fields of oncology and pain management that a bisphosphonate can relieve pain as a consequence of its an anti-tumor effect. Second Pappagallo Dec. at 13.

- The mechanism for the pain relief sometimes observed in cancer patients who are administered a bisphosphonate for treatment of their cancer was believed to be the relief of pressure on surrounding tissues as a consequence of a reduction in tumor mass. Second Pappagallo Dec. at 14.
- It was not known or predictable in the fields of oncology and pain management that a bisphosphonate can relieve pain independent of its anti-tumor effect. Second Pappagallo Dec. at 15.
- Because pain relief in cancer patients treated with a bisphosphonate is believed to be related to tumor shrinkage, one of ordinary skill in the art would not have reasonably predicted that a bisphosphonate can have a pain relieving effect in a patient not suffering from cancer. Second Pappagallo Dec. at 16.
- Upon reading Urban as a whole, one of ordinary skill in the art would understand this reference to describe a rat bone cancer model in which zoledronate, a bisphosphonate, had a pain-relieving effect as a result of its known anti-tumor effects. Second Pappagallo Dec. at 17.
- Reading the reference as a whole, one of ordinary skill in the art would not have understood Urban to disclose, suggest, or predict that a bisphosphonate can have a pain-relieving effect in a cancer-free rat or other cancer-free mammal. Second Pappagallo Dec. at 18.

Bader does not provide the missing teaching that a bisphosphonate can have a pain-relieving effect in a cancer-free mammal. Thus, no combination of the references suggests or would lead one of ordinary skill in the art to predict that a bisphosphonate can relieve pain independent of its anti-tumor effect. No combination of the references suggests that a known cancer-killing agent, i.e., a bisphosphonate, would have an anti-nociceptive effect in a subject with pain unrelated to cancer. Accordingly, the instant claims are non-obvious because "chronic spinal mechanical pain" excludes back pain caused by cancer. *See*, specification, page 7, lines 15-16.

For the reasons stated above, this rejection should be withdrawn.

Conclusion

In view of the above remarks, it is respectfully requested that the pending claims be allowed and the case passed to issue.

If there are any other issues remaining, which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: February 17, 2009

Respectfully submitted,

By _____

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Docket No.: 05986/100K504-US1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Marco PAPPAGALLO

Application No.: 10/624,942 Confirmation No.: 7691

Filed: July 21, 2003 Art Unit: 1617

For: TREATMENT OF SPINAL MECHANICAL PAIN Examiner: Jennifer M. KIM

SECOND DECLARATION OF DR. MARCO PAPPAGALLO UNDER 37 C.F.R. 1.132

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Marco Pappagallo, declare that:

1. I am a U.S. citizen and am more than twenty-one years of age.

2. I am the inventor of the above-referenced application.

3. I presently hold the position of Director of Pain Medicine Research and Development at Mount Sinai School of Medicine in New York, New York. I am also a Professor of Anesthesiology in the Department of Anesthesiology and Pain Medicine at the Mount Sinai School of Medicine.

4. I received my medical degree from the University of Rome in 1982, and completed my residency in neurology at the State University of New York at Stony Brook in 1990. I was a clinical and research fellow in pain medicine at The Johns Hopkins Pain Treatment Center in Baltimore Maryland from 1990 to 1993.

5. I have been an attending physician since 1993.

6. From 2003 to 2006, I have been an attending physician in the Department of Pain Medicine & Palliative Care at Beth Israel Medical Center in New York, New York.

7. From 2006 to the present, I have been an associate attending physician in the Department of Anesthesiology at Mount Sinai Hospital in New York, New York.

8. A copy of my curriculum vitae was submitted to the U.S. Patent Office in this application on June 6, 2007.

9. I have read and am familiar with the above-referenced application and its file history, including the Office Action mailed October 15, 2008 and the Advisory Action mailed December 23, 2008.

10. I have read and am familiar with Urban et al., Society for Neuroscience Abstracts, 2001;27(1):1326 ("Urban").

11. It is my understanding that a prior art reference must be considered in its entirety.

12. Prior to July 24, 2002, it was well-known in the fields of oncology and pain management that a bisphosphonate, such as zoledronate, can have an anti-tumor effect.

13. Prior to July 24, 2002, it was known in the fields of oncology and pain management that a bisphosphonate can relieve pain as a consequence of its an anti-tumor effect.

14. As of July 24, 2002, the mechanism for the pain relief sometimes observed in cancer patients who are administered a bisphosphonate for treatment of their cancer was believed to be the relief of pressure on surrounding tissues as a consequence of a reduction in tumor mass.

15. Prior to July 24, 2002, it was not known or predictable in the fields of oncology and pain management that a bisphosphonate can relieve pain independent of its anti-tumor effect.

16. Because pain relief in cancer patients treated with a bisphosphonate is believed to be related to tumor shrinkage, one of ordinary skill in the art would not have reasonably predicted as of

July 24, 2002 that a bisphosphonate would have a pain relieving effect in a patient not suffering from cancer.

17. As of July 24, 2002, one of ordinary skill in the art reading Urban as a whole would have understood Urban as describing a rat bone cancer model in which the known anti-tumor effect of zoledronate, a bisphosphonate, had a pain-relieving effect.

18. As of July 24, 2002, one of ordinary skill in the art, reading the reference as a whole, would not have understood Urban to disclose, suggest, or predict that a bisphosphonate would have a pain-relieving effect in a cancer-free rat or other cancer-free mammal.

19. I declare further that statements made in this declaration of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Dated: 2/11/09

Marco Pappagallo, M.D.